A Comparative Study of White Light Endoscopy, Chromoendoscopy and Magnifying Endoscopy with Narrow Band Imaging in the Diagnosis of Early Gastric Cancer after Helicobacter pylori Eradication

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INTRODUCTION

Helicobacter pylori (H. pylori) infection is well accepted as a risk factor for the development of gastric cancer [1-3] and a prospective study conducted in Japan demonstrated that H. pylori eradication therapy significantly reduced the incidence of metachronous gastric cancer following endoscopic resection of early-stage gastric cancer (EGC) [4]. Therefore, the Japanese national health insurance system has recently covered the cost for the eradication therapy for patients with H. pylori-associated gastritis. However, gastric cancer is discovered in patients even after successful H. pylori eradication [5]. Moreover, H. pylori eradication influences the clinicopathological features of gastric tumors, including macro- and microscopic appearances [6-10]. Gastric cancer found after H. pylori eradication appears with indistinct forms, such as tiny and flattened lesions [6-8]. Histopathological findings of gastric cancer after H. pylori eradication are characterized as either regenerating non-tumorous epithelium covering over the tumorous tissue and/or surface differentiation of tumors [8-10], which may confuse endoscopic as well as histologic diagnosis [7, 9, 10]. This evidence suggests that EGC after H.

ABSTRACT

Background & Aim: Early-stage gastric cancer (EGC) found after H. pylori eradication often has non-tumorous epithelium on the tumorous tissue and/or surface differentiation of tumors, which may confuse endoscopic and histologic diagnosis. We investigated the diagnostic reliability of EGC using conventional white light endoscopy (WLE), chromoendoscopy (CE) using indigo carmine, and magnifying endoscopy with narrow band imaging (ME-NBI) in patients with EGC with or without history of prior H. pylori eradication therapy.

Methods: Diagnostic reliability of EGC by using the WLE, CE and ME-NBI was investigated in 71 EGC lesions diagnosed after successful H. pylori eradication (eradication group) and 115 EGC lesions with current H. pylori infection (control group).

Results: Diagnostic reliability of EGC was lower in the eradication group than in the control group using all three modalities. In particular, the diagnostic accuracy of CE in the eradication group was especially lower compared to that of the control group (WLE: 74.6% vs. 86.1%, P=0.05; CE: 64.8% vs. 91.3%, P<0.0001; ME-NBI: 88.7% vs. 98.2%, P=0.01). The ME-NBI scored better in comparison with WLE and CE in the eradication group (both P<0.05). The indistinct EGC lesions in the eradicated group by using CE were associated with the presence of histological changes such as non-tumorous epithelium on the tumor and/or surface differentiation of tumors (P=0.005).

Conclusions: It should be noted that the diagnostic reliability of EGC after H. pylori eradication becomes lower especially using CE. Indistinguishable cases using CE are associated with histological findings such as non-tumorous epithelium on the tumor and/or surface differentiation of tumors.

Key words: Gastric cancer – H. pylori – eradication – diagnostic reliability – magnifying endoscopy with narrow band imaging – white light endoscopy – chromoendoscopy.
pylori eradication might need alternative diagnostic strategy for the precise endoscopic diagnosis. To establish endoscopic diagnostic strategy for EGC after H. pylori eradication, we evaluated the diagnostic reliability of conventional white light endoscopy (WLE), chromoendoscopy (CE) using indigo carmine dye and magnifying endoscopy with narrow band imaging (ME-NBI) in patients with EGC after H. pylori eradication. We also compared this reliability in cases without history of prior H. pylori eradication therapy.

**PATIENTS AND METHODS**

**Study population**
We studied 71 EGCs from 61 consecutive patients diagnosed at least 6 months after the successful H. pylori eradication therapy for various reasons, including gastric and duodenal ulcer or scarring and chronic gastritis, or after endoscopic resection of EGC (eradication group). Median post-eradication period was 36 months (ranging between 6 and 180 months). We also included 115 EGCs from 104 consecutive patients who had H. pylori infection at registration as the control group. Six lesions from 6 patients in the eradication group were metachronous cases from the control group who were diagnosed after initial endoscopic submucosal dissection (ESD) and subsequent successful H. pylori eradication. These patients were partly recruited from our other study investigating the clinico-pathological characteristics of EGC in relation to the history of successful H. pylori eradication [7]. All patients attended the endoscopy center of Fujita Health University for the ESD between April 2011 and December 2016. In both groups, age and sex were registered based on the medical record. Anatomical location and color were investigated based on the endoscopic image obtained during the esophagogastroduodenoscopy (EGD) examination before ESD. Fujita Health University School of Medicine approved the protocol, and written informed consent was obtained from all participating subjects.

**Endoscopic procedure and image evaluation of EGC by using WLE, CE, and ME-NBI**
The video endoscope used in this study was an Olympus GIF-H260Z and a CV260SL/CV290SL (Olympus Medical Systems, Tokyo, Japan). Initially, endoscopic pictures for each lesion were taken in the order of WLE then CE using indigo carmine dye (0.2%). All these procedures were performed without magnification view. Then, the surface patterns of each lesion were carefully evaluated by ME-NBI with high power magnification. Endoscopic pictures covering the entire lesion using the ME-NBI were also taken and stored for review. All endoscopic procedures were performed by two experienced endoscopists (T.T. and N.H.). The diagnostic utility of the conventional WLE, CE and the ME-NBI was determined in terms of diagnostic reliability of EGC. All image evaluation was performed real time during the examination. This image evaluation was always performed first by WLE endoscopy, followed by the CE and the ME-NBI, in this order. We recorded all results immediately and did not change them even if a different diagnosis was made by other modalities.

The recorded endoscopic pictures, as well as reports on image interpretation were also reviewed by another endoscopist in order to evaluate their reasonability. If their opinions did not agree, a final judgment was arrived at by consensus following the discussion of each individual case. Diagnostic reliability of EGC using the conventional WLE and the CE was based on the presence of well-demarcated, depressed, or elevated lesions with an irregular margin and an irregular mucosal area with a color change (reddish or whitish), while no evidence of such findings was considered to be a non-cancerous lesion by the conventional WLE and the CE. The diagnostic criteria of EGC using ME-NBI have been reported as the vessel plus surface (VS) classification system [11-14]. In this system, endoscopic diagnosis of EGC is performed in terms of microvascular (MV), microsurface (MS) patterns and presence of demarcation line (DL). Diagnosis of EGC using the ME-NBI was based on the presence of irregular MV and/or MS with clear DL, while no evidence of such findings was considered to be a non-cancerous lesion by the ME-NBI.

**Evaluation of H. pylori status**
Evaluation of H. pylori eradication treatment in the eradication group was based on the urea breath test as well as the histological assessment using endoscopic biopsy specimens obtained from non-pathological mucosa of the greater curvature of gastric antrum and upper corpus. If the results were negative in both examinations, we considered that H. pylori eradication had been successfully performed. All patients from the control group were H. pylori positive based on either the 13C-urea breath test, serum antibody titer or histological assessment. We considered H. pylori as positive if at least one of these tests was positive. All the above evaluations were performed at enrolment in the study.

**Histological assessment of endoscopic biopsy**
We reported that the diagnosis of neoplastic or non-neoplastic lesion by endoscopic biopsy is often difficult in EGC after H. pylori eradication, possibly due to the normal epithelium or surface differentiation covering the cancerous tissues [7]. We therefore investigated the prevalence of inconclusive diagnosis of EGC during the pre-treatment endoscopic biopsy. We defined an inconclusive diagnosis of EGC as a biopsy material for which diagnosis of neoplastic or non-neoplastic lesions is difficult despite sufficient amount of tissue. This analysis was based on the report from senior pathologists in our hospital.

**Histological assessment of resected specimens**
Histological assessment of resected specimens including histologic subtypes and depth were defined according to the Japanese Classification of Gastric Carcinoma, 14th edition [15]. All EGC lesions were histologically diagnosed as differentiated adenocarcinoma. Distinct histologic changes of gastric cancer after H. pylori eradication are characterized as either regenerating non-tumorous epithelium covering over the tumorous tissue and/or surface differentiation of tumors [8-10], which may influence the endoscopic or histological diagnosis using the endoscopic biopsy. We investigated these histopathological characteristics in the EGC lesions. We
accounted these histopathological features if approximately more than 30% of the entire area was evident and defined such cases as having histologic changes after *H. pylori* eradication. This analysis was based on the report from senior pathologists in our hospital.

**Statistical analysis**
Continuous variables between the two groups were determined using the Student’s t-test. Unmatched and matched categorical variables were determined using the Chi-square test and the McNemar test, respectively. Differences at P values less than 0.05 were considered to be statistically significant.

**RESULTS**

**Clinico-pathological characteristics of the patients**
Detailed clinico-pathological characteristics of EGC from the eradication and control groups are summarized in Table I. Age, gender, location, tumor size and depth were not significantly different between the two groups. The EGC lesions from the eradication group were significantly associated with depressed morphology (P<0.0001) and reddish color (P=0.02), which was in line with other studies [6, 7]. Inconclusive diagnosis by initial endoscopic biopsy (P<0.0001) was also significantly more frequent in the eradication group than in the control group. Moreover, histological assessment of resected specimen showed that presence of regenerating non-tumorous epithelium covering over the tumorous tissue and/or surface differentiation of tumors was significantly more frequent in the eradication group than in the control group (P<0.0001).

**Diagnostic reliability of WLE, CE and ME-NBI for predicting EGC**

The diagnostic reliability in predicting EGC for the WLE, CE and ME-NBI was 74.6%, 64.8% and 88.7% in the eradication group and 86.1%, 91.3% and 98.2% in the control group, respectively (Table II). In the comparison of eradication and control groups, the diagnostic reliability of EGC was lower in the eradication group than in the control group for all three modalities of investigation. In particular, the diagnostic accuracy of CE in the eradication group was especially lower compared to that in the control group (WLE, P=0.05; CE, P<0.0001; ME-NBI, P=0.007).

Comparing the diagnostic reliability in the eradication group, ME-NBI better scored in comparison with WLE and CE (all P<0.05) (Table III). The diagnostic reliability of ME-NBI tended to be higher compared to the WLE and CE in the control group. The diagnostic reliability of CE also tended to be higher compared to the WLE in the control group (P=0.08). However, in the eradication group, the diagnostic reliability of CE tended to be rather lower compared to that of WLE (P=0.07).

**Table I. Clinico-pathological characteristics among eradication and control groups**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Eradication group (71 lesions/61 patients)</th>
<th>Control group (115 lesions/104 patients)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>71 (53-87)</td>
<td>72 (53-89)</td>
<td>0.44</td>
</tr>
<tr>
<td>Males n (%)</td>
<td>42 (68.9)</td>
<td>82 (78.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Median post-eradication period at diagnosis (range)</td>
<td>36 months (6-180)</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Location: U/M/L n (%)</td>
<td>10/27/34 (14.1/38.0/47.9)</td>
<td>13/4/58 (11.3/38.3/50.4)</td>
<td>0.85</td>
</tr>
<tr>
<td>Morphology* Protruding/depressed n (%)</td>
<td>10/61 (14.1/85.9)</td>
<td>53/62 (46.1/53.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Color: Redness/Whiteness/same as surroundings n (%)</td>
<td>52/109 (73.2/14.1/12.7)</td>
<td>61/34/20 (53.0/29.6/17.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Tumor size: ±SE</td>
<td>12×0.1×2mm</td>
<td>13.4×0.6mm</td>
<td>0.25</td>
</tr>
<tr>
<td>Depth**: M/SM1/SM2 n (%)</td>
<td>63/4/4 (88.8/5.6/5.6)</td>
<td>105/73 (91.3/6.1/2.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Inconclusive diagnosis by initial endoscopic biopsy n (%)***</td>
<td>19/70 (27.1)</td>
<td>2/112 (1.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of regenerating non-tumorous epithelium covering over the tumorous tissue and/or surface differentiation of tumors n (%)</td>
<td>40/71 (56.3)</td>
<td>10/115 (8.7)</td>
<td>&lt;0.0001</td>
</tr>
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* Protruding, 0-I, 0-IIa; depressed, 0-IIc, 0-IIa+IIc, 0-IIc+IIa according to the Japanese classification; ** SM1, cases with submucosal invasion less than 500 μm; SM2, cases with submucosal invasion greater than 500 μm; ***1 case of eradication group did not undergo pre-treatment endoscopic biopsy; in 3 cases of control group sufficient biopsy samples could not be obtained. Age, tumor size were compared using Student’s t-test. Location, morphology, color and depth and unexpected SM2 case were using Chi statistics.

**Table II. Diagnostic reliability of early gastric cancer using WLE, CE and ME-NBI**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Eradication group vs. Control group</th>
<th>P (eradication group vs. control group)</th>
</tr>
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<tbody>
<tr>
<td>WLE</td>
<td>53/71 (74.6%)</td>
<td>99/115 (86.1%)</td>
</tr>
<tr>
<td>CE</td>
<td>46/71 (64.8%)</td>
<td>105/115 (91.3%)</td>
</tr>
<tr>
<td>ME-NBI</td>
<td>63/71 (88.7%)</td>
<td>113/115 (98.2%)</td>
</tr>
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</table>

**Table III. Comparison of diagnostic reliability of early gastric cancer among different modalities**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Eradication group vs. CE</th>
<th>WLE vs. ME-NBI</th>
<th>CE vs. ME-NBI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication group</td>
<td>P=0.07</td>
<td>P=0.02</td>
<td>P=0.0005</td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>P=0.08</td>
<td>P=0.07</td>
<td></td>
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</table>

WLE, white light endoscopy; CE, chromoendoscopy; ME-NBI, Magnifying narrow-band imaging; Statistical analysis performed by the Chi square test.

**The association between histologic changes after *H. pylori* eradication and inconclusive diagnosis of EGC by the endoscopic biopsy**

It has been reported that gastric cancer after *H. pylori* eradication often has distinct histological characteristics.
such as regenerating non-tumorous epithelium covering over the tumorous tissue and/or surface differentiation of tumors [9, 10], which may confuse the endoscopic diagnosis. We investigated the association between indistinct cases of EGC lesions from the eradication group and the presence of regenerating non-tumorous epithelium and/or surface differentiation of tumors. This analysis showed that the presence of regenerating non-tumorous epithelium and/or surface differentiation of tumors was significantly associated with indistinct EGC cases especially by using the CE (P=0.003) (Table IV and Fig.1).

**DISCUSSION**

We showed that the diagnostic reliability of EGC was significantly lower in the eradication group compared to the control group. In particular, the diagnostic accuracy of CE in the eradication group was lower compared to that of the control group. The EGC lesions that were considered to be indistinct by the CE were significantly associated with the presence of histological changes such as regenerating non-tumorous epithelium on the tumorous tissue and/or surface differentiation of tumors.

Early gastric cancer after *H. pylori* eradication is reported as flattened and indistinct forms, which make endoscopic diagnosis difficult [7, 9, 10]. The normal epithelium and/or surface differentiation covering the tumor tissue has also been reported as the typical histopathological findings of gastric cancer after *H. pylori* eradication [8-10]. It is possible that such histopathological changes after *H. pylori* eradication make the EGC lesion indistinguishable from the surrounding non-neoplastic mucosa. In this study, prevalence of inconclusive diagnosis by the endoscopic biopsy was significantly higher in the eradication cases than in controls, which was similar to our recent study [7]. Since the tumor surface in the eradication group is often covered by the normal epithelium or low grade neoplastic tissue by the surface differentiation, it is possible that the portion of carcinoma tissue would become smaller despite the fact that sufficient amount of tissue was obtained by the endoscopic biopsy. Thus, the histological condition shown in the eradication group would be also relevant to the high incidence of inconclusive diagnosis by the endoscopic biopsy.

Diagnostic reliability of EGC using the conventional WLE and the CE is based on endoscopic findings of irregularly shaped depression or unevenness elevation, which are often accompanied with a color change (reddish or whitish). Compared to the conventional WLE, the CE can more enhance the depression or elevation in the EGC lesions by using the indigo carmine dye, while the information of color would become indistinct by its dark blue color. Since the EGC lesion in the eradication group often appeared as a red color depressed lesion [7, 9], it would be very important to detect such color change by using the WLE to diagnose EGC after *H. pylori* eradication. On the other hand, it is possible

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<th>Table IV. Association between regenerating non-tumorous epithelium and/or surface differentiation of tumors and indistinct cases in the eradication group</th>
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<tbody>
<tr>
<td>Regenerating non-tumorous epithelium and/or surface differentiation of tumors</td>
</tr>
<tr>
<td>Present (n=40)</td>
</tr>
<tr>
<td>12/40 (30.0%)</td>
</tr>
<tr>
<td>Absent (n=31)</td>
</tr>
</tbody>
</table>

WLE, white light endoscopy; CE, chromoendoscopy; ME-NBI, Magnifying narrow-band imaging; WLE: P=0.31, CE: P=0.005, ME-NBI: P=0.70, Statistical analysis performed by Chi statistics.

**Fig. 1.** A case of EGC after *H. pylori* eradication. A slightly depressed lesion with red color change (white arrowheads) is seen by using white light endoscopy (WLE) (a), while the lesion becomes unclear using the chromoendoscopy (CE) with indigo carmine dye (b). Magnifying endoscopy with magnifying endoscopy with narrow band imaging (ME-NBI) demonstrated irregular micro vascular (MV) pattern with clear demarcation line (DL) (c). The histological assessment (H&E x4)of resected specimen showed neoplastic crypts (black arrowhead) interspersed within regenerating non-tumorous epithelium (d).
that histological changes such as normal epithelium and/or surface differentiation covering the tumor tissue would make the depression or elevation unclear in the eradication cases. Therefore, it should be noted with caution that, in considerable EGCs in eradicated cases, the endoscopic diagnosis would become rather difficult by using indigo carmine dye.

The ME-NBI scored better in comparison with the WLE and the CE in both the eradication and control groups. The diagnostic reliability of ME-NBI in the eradication group seemed to be acceptable with a diagnostic reliability of 89.1%, although it was lower than that of the control group. ME-NBI visualizes the fine mucosal and its capillary patterns. The diagnostic performance of the ME-NBI has been demonstrated across a variety of gastrointestinal neoplasms [14,16-18]. Our data indicates that ME-NBI allows to distinguish well the EGC lesion irrespective of H. pylori eradication status. On the other hand, it has been reported that a considerable percentage of EGCs after H. pylori eradication show “gastritis-like pattern” resembling the surrounding non-cancerous mucosa even by using ME-NBI [9, 10]. In our study, an EGC lesion in the eradication group that could be diagnosed by the M-NBI (89.1% of cases) demonstrated suggestive endoscopic findings of the EGC, such as irregular MV and/or MS with clear DL, at least in part of the tumor. This suggests that the diagnostic performance of ME-NBI is favorable at least for the detection of EGC in the eradication cases. Our data also proposes a diagnostic algorithm by combining WLE and ME-NBI to precisely diagnose EGC lesions after H. pylori eradication. On the other hand, the indistinct EGC lesions of the eradication group [9, 10] would be associated with difficulty in diagnosing their horizontal extent. Since the precise assessment of the horizontal extent of the EGC is important for ESD, well-designed studies would be also needed to establish the diagnostic strategy for the horizontal extent of the EGC after H. pylori eradication.

In Japan, the pathological diagnosis of EGC is based on the Japanese Classification of Gastric Carcinoma [15]. According to the International Union Against Cancer (UICC)/TNM classification, the mucosal cancer (M) in the Japanese classification would be equivalent to either Tis or T1a in the UICC/TNM classification, while submucosal cancer (SM1 and SM2) in the Japanese classification would be equivalent to T1b in the UICC/TNM classification. Since the majority of cases in our study were mucosal cancers, our result would be useful for endoscopists all over the world to diagnose gastric cancer at early stage. Because this is a study conducted in a single institution, and there was a small number of cases, and there may be the bias of the preoperative biopsy, our preliminary results need to be confirmed by randomized controlled trials using a larger cohort to establish diagnostic strategy for EGC after H. pylori eradication.

CONCLUSION

Our data indicates that the diagnostic reliability is significantly lower in eradication cases especially using the CE. This indicates that combining the WLE and ME-NBI would provide precise diagnosis of EGC after H. pylori eradication. The current findings will provide useful information for the endoscopist for a more appropriate endoscopic diagnosis of EGC based on the H. pylori eradication status.

Conflicts of interest: No conflicts of interest exist.

Authors’ contribution: N. H., T. K., M. O., and T. S. collected clinical data. N. H. and T. T. performed endoscopic examination, analyzed the results and wrote the manuscript. M. N., Y. N., and N. O. supervised the data analysis and manuscript preparation. S. T. advised about pathological interpretation.

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